

Remarks

Claims 1-40 were pending in this application. Claims 1, 10, 17, 23, 30, and 32 have been amended, claims 2, 9, and 22 have been canceled herein without prejudice, and no claims have been added. Reconsideration of this application is respectfully requested in light of the above amendments and the following remarks.

Rejection of Claims 1-40 Under 35 U.S.C. §112

Claims 1-40 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner states that the claims “are confusing because they simultaneously require a substrate and then detachment from the substrate.” In response, Applicants have amended independent claims 1, 17, and 32 to clarify that cardiac cells are provided on the substrate and form a confluent monolayer thereon, and then subsequently the monolayer detaches from the substrate and self-organizes to form a three-dimensional cardiac muscle construct (*see* p. 7, lines 21-30; p.9, line 18-p. 10, line 3). Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner also states that the terms “scaffold-free substrate” and “in the absence of a scaffold” are indefinite. In response, Applicants have amended independent claims 1, 17, and 32 to recite that cardiac cells are provided on the substrate “without disposing the cells within an exogenous scaffold material”, support for which can be found, for example, at p. 2, line 26 - p. 3, line 3 of the specification. Accordingly, reconsideration and withdrawal of this rejection is also respectfully requested.

With regard to the Examiner’s confusion over the term “anchors”, Applicants have amended independent claims 1, 17, and 32 to recite “at least two anchors secured to the substrate in spaced relationship . . . wherein at least some of the cells are in contact with the anchors . . . wherein the anchors are receptive to the cells and allow the cells to attach thereto to form a confluent monolayer between the anchors, and subsequently permitting the monolayer to detach from the substrate.” Support for this amendment can be found, for

example, at p. 8, lines 13-25 and p. 9, lines 1-3 of the specification. As is known to those skilled in the art, an anchor is a material or structure used at the interface of engineered tissue which is used to provide mechanical, chemical, or other cues to the tissue to promote the organization of the tissue. In contrast, a scaffold is understood by those skilled in the art to be a three-dimensional growth surface into which cells are introduced and which serves to at least partially stand in place of naturally generated extracellular matrix materials. In the system and method of the present invention, the anchors do not extend into the space occupied by the self-organizing tissue, and thus cannot be confused with a scaffold. Furthermore, Applicants' specification is clear on the distinction between anchors and scaffold material. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

With reference to the rejection of claim 30, Applicants have amended this claim herein to delete the word "suitable". Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of this claim.

Lastly, Applicants respectfully traverse the rejection of claim 32 under 35 U.S.C. §112. While cells themselves are three-dimensional, in tissue engineering the term "three-dimensional" distinguishes the resulting construct shape from planar cell monolayers which are taken to be two-dimensional as is known to those skilled in the art. Therefore, reconsideration and withdrawal of the rejection of this claim is also respectfully requested.

**Rejection of Claims 1-5, 8, 15, 17-19, 32-34, 37, and 40
Under 35 U.S.C. §102(b) Over Malette**

Claims 1-5, 8, 15, 17-19, 32-34, 37, and 40 have been rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,605,623 issued to Malette et al. ("Malette"). Applicants have amended claims 1, 17, and 32 herein to more particularly point out and distinctly claim the subject matter of the invention.

As described above, the claims now recite "cardiac cells provided on the substrate without disposing the cells within an exogenous scaffold material" such that the cell monolayer can "detach from the substrate and self-organize to form a three-dimensional

cardiac muscle construct.” As is known in the art, “self-organizing” refers to tissues wherein the cells themselves, and not a pre-existing scaffold, define the size and shape of the resulting tissue construct as the cells transform from a principally two-dimensional monolayer configuration into a three-dimensional configuration separated physically from the substrate. In contrast to Applicants’ claimed invention, Malette utilizes a chitosan scaffold material to form his three-dimensional tissue (*see* Malette, col. 1, lines 44-47 and 57-58; col. 3, lines 4-39). In Applicants’ specification, the differences between the prior art, including Malette, and the claimed invention are discussed:

For cardiac muscle, U.S. Patent No. 4,605,623 issued to Malette et al., for example, describes a method for cultivating the three-dimensional growth of cardiac myocytes within a chitosan scaffold material. Although this and other scaffold-based cardiac tissue constructs have been reported (*see* Atkins (sic) et al., *Tissue Eng* 5, 103-18, Apr 1999; . . . Zimmerman et al., *Circ Res* 90, 223-30, Feb 2002; . . .), the creation of a self-organizing contractile cardiac muscle construct in culture has proven elusive (p. 2, line 5-19).

The present invention provides a system and method for culturing cardiac cells in such a way as to promote the self-organization of a three-dimensional, contractile cardiac muscle construct in culture. The contractile constructs do not employ an artificial scaffold in their contractile region; rather, the construct self-organizes from a cohesive monolayer of cardiac myocytes and fibroblasts (p. 6, lines 6-11; FIGS. 1A-1C).

Malette does not disclose or suggest “cardiac cells provided on the substrate without disposing the cells within an exogenous scaffold material” nor a cell monolayer able to “detach from the substrate and self-organize to form a three-dimensional cardiac muscle construct” as claimed by Applicants. Therefore, claims 1, 17, and 32 are patentably distinguishable over Malette, and Applicants respectfully request reconsideration and withdrawal of the rejection of these claims, along with their corresponding dependent claims, under 35 U.S.C. §102(b).

**Rejection of Claims 1-9, 12-13, 15, 17-22, 25-26 and 32-37
Under 35 U.S.C. §102(b) Over Zimmerman 2000**

Claims 1-9, 12-13, 15, 17-22, 25-26 and 32-37 have been rejected under 35 U.S.C. §102(b) as being anticipated by Zimmerman et al., *Biotechnology & Bioengineering* 2000 (“Zimmerman 2000”). As explained above, claims 1, 17, and 32 have been amended to recite “cardiac cells provided on the substrate without disposing the cells within an exogenous scaffold material” wherein the cell monolayer is able to “detach from the substrate and self-organize to form a three-dimensional cardiac muscle construct.” In contrast, Zimmerman 2000 discloses culturing cardiac myocytes in a 3-dimensional collagen/Matrigel matrix (*see* Zimmerman 2000, p. 106, col. 2, ¶2; p. 107, col. 1, ¶4; FIG. 1). For the reasons described with reference to Malette, Applicants’ claimed invention is patentably distinguishable over Zimmerman 2000, and reconsideration and withdrawal of this rejection is respectfully requested.

**Rejection of Claims 1-9, 12, 15, 17-22, 25 and 32-40
Under 35 U.S.C. §102(b) Over Zimmerman 2002**

Claims 1-9, 12, 15, 17-22, 25, and 32-40 have been rejected under 35 U.S.C. §102(b) as being anticipated by Zimmerman et al., *Circulation Research* 2002 (“Zimmerman 2002”). As with Zimmerman 2000, Zimmerman 2002 discloses disposing cardiac myocytes within a collagen/Matrigel matrix (*see* Zimmerman 2002, p. 224, col. 1, ¶3). Accordingly, the claims are patentably distinguishable over Zimmerman 2002, and Applicants respectfully request reconsideration and withdrawal of this rejection.

**Rejection of Claims 1-5, 7-9, 12, 17-19, 21, 25, 32-34, 36, and 38-39
Under 35 U.S.C. §102(b) Over Akins**

Claims 1-5, 7-9, 12, 17-19, 21, 25, 32-34, 36, and 38-39 have been rejected under 35 U.S.C. §102(b) as being anticipated by Akins et al. (“Akins”). Once again, Akins disposes cells within an exogenous scaffold material in the form of polystyrene microcarrier beads and oriented collagen fibers (*see* Akins, p. 105, ¶2; FIG. 1B). For the reasons explained above, claims 1, 17, and 32 are patentably distinguishable over Akins, and reconsideration and

withdrawal of the rejection of these claims, as well as their corresponding dependent claims, is respectfully requested.

**Rejection of Claims 1-3, 5-6, 12, 17-18, 20, 25, 32, 34-35, and 39
Under 35 U.S.C. §102(b) Over Shimizu 2000**

Claims 1-3, 5-6, 12, 17-18, 20, 25, 32, 34-35, and 39 have been rejected under 35 U.S.C. §102(b) as being anticipated by Shimizu, Igaku no Ayumi 2000 ("Shimizu 2000"). As described above, Applicants claim a system and method wherein the cell monolayer detaches from the substrate and self-organizes to form a three-dimensional cardiac muscle construct. In contrast, Shimizu 2000 discloses a cell layering technique wherein cardiac myocyte sheets are layered on top of each other to form a three-dimensional cardiac tissue (*see* Shimizu 2000, p. 3). Shimizu's monolayers are not self-organizing to form a three-dimensional construct as in Applicants' claimed invention, but rather are simply layered on top of each other to create a three-dimensional structure. As such, claims 1, 17, and 32 are patentably distinguishable over Shimizu 2000, and Applicants respectfully request reconsideration and withdrawal of the rejection of these claims and their corresponding dependent claims.

**Rejection of Claims 1-3, 5-6, 12, 17-18, 20, 25, 30, 32, 34-35, and 39
Under 35 U.S.C. §102(b) Over Shimizu 2003**

Claims 1-3, 5-6, 12, 17-18, 20, 25, 30, 32, 34-35, and 39 have been rejected under 35 U.S.C. §102(b) as being anticipated by Shimizu, Biomaterials 2003 ("Shimizu 2003"). As with Shimizu 2000, Shimizu 2003 describes cell sheet layering to create three-dimensional tissues, rather than the self-organizing of a single monolayer to form a three-dimensional cardiac muscle construct as claimed by Applicants (*see* Shimizu 2003, p. 2312, col. 1, ¶1; FIG. 4). Therefore, Applicants' claimed invention is patentably distinguishable over Shimizu 2003, and reconsideration and withdrawal of this rejection is also respectfully requested.

Rejection of Claims 1-27, 29, and 32-40 Under 35 U.S.C. §103(a)

Claims 1-27, 29 and 32-40 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Malette or Zimmerman 2000 or Zimmerman 2002 or Akins or Shimizu 2000 or Shimizu 2003 in view of U.S. Patent No. 6,207,451 issued to Dennis et al. ("Dennis '451"). As explained above, none of Malette, Zimmerman 2000, Zimmerman 2002, Akins, Shimizu 2000 or Shimizu 2003 disclose or suggest a system and method including "cardiac cells provided on the substrate without disposing the cells within an exogenous scaffold material" allowing the cell monolayer to "detach from the substrate and self-organize to form a three-dimensional cardiac muscle construct", nor does Dennis '451 provide the disclosure absent in these references. Therefore, claims 1-27, 29, and 32-40 are patentably distinguishable over Malette, Zimmerman 2000, Zimmerman 2002, Akins, Shimizu 2000 and Shimizu 2003, either alone or in combination with Dennis '451, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-29 and 32-40 Under 35 U.S.C. §103(a)

Claims 1-29 and 32-40 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Malette or Zimmerman 2000 or Zimmerman 2002 or Akins or Shimizu 2000 or Shimizu 2003 in view of Dennis '451 and further in view of U.S. Patent No. 6,303,286 issued to Dennis et al. ("Dennis '286"). As above, Malette, Zimmerman 2000, Zimmerman 2002, Akins, Shimizu 2000 and Shimizu 2003 do not disclose or suggest Applicants' claimed invention, nor do Dennis '451 or Dennis '286 provide the disclosure absent in these references. Therefore, claims 1-29 and 32-40 are patentably distinguishable over Malette, Zimmerman 2000, Zimmerman 2002, Akins, Shimizu 2000 and Shimizu 2003, either alone or in combination with Dennis '451 and Dennis '286, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-27 and 29-40 Under 35 U.S.C. §103(a)

Claims 1-27, 29 and 32-40 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Malette or Zimmerman 2000 or Zimmerman 2002 or Akins or Shimizu 2000 or Shimizu 2003 in view of US2001/0049138 to Dennis et al. ("Dennis '138"). Once again,

none of the primary references disclose or suggest "cardiac cells provided on the substrate without disposing the cells within an exogenous scaffold material" wherein the monolayer can "detach from the substrate and self-organize to form a three-dimensional cardiac muscle construct", nor does Dennis '138 provide the disclosure absent in these references. Therefore, claims 1-27, 29 and 32-40 are patentably distinguishable over Malette, Zimmerman 2000, Zimmerman 2002, Akins, Shimizu 2000 and Shimizu 2003, either alone or in combination with Dennis '138, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

In summary, Applicants believe that the claims meet all formal and substantive requirements and that the case is in appropriate condition for allowance. Accordingly, such action is respectfully requested. If a telephone conference would expedite allowance of the case or resolve any further questions, such a call is invited at the Examiner's convenience.

Please charge the Petition fee of **\$60.00**, as well as charge any additional fees or credit any overpayments as a result of the filing of this paper, to our Deposit Account No. 02-3978.

Respectfully submitted,

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